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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,061	04/04/2005	John Sidney	2060.0330002/EKS/MM	7448

26111 7590 05/01/2007
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EXAMINER	
BRISTOL, LYNN ANNE	

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
05/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,061	SIDNEY ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *2,16,17 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-15 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-19 are all the pending claims for this application.

2. The amendment to the specification of 4/4/05 to cross-reference the related applications has been entered. The amendment to the specification of 3/6/06 to include a reference to the sequence listing has been entered.

Election/Restrictions

3. Applicant's election with traverse of Group I (Claims 1, 3-15 and 18) and species for peptides of SEQ ID NO: 53, 55, 139, 502, 527, 627, 673, 807, 846 and 859 and species for antigen of papilloma virus in the reply filed on 2/23/07 is acknowledged. The traversal is on the ground(s) that searching the elected group and elected peptides would not entail a serious burden and would reveal publications disclosing the subject matter for each of the non-elected groups. This is not found persuasive because the composition claims of Group II are drawn to a composition with different elements than those of Group I. With respect to each of the method inventions of Groups III-VI, the methods require different steps and reagents and can be practiced with materially different reagents in order to achieve the intended endpoint for the intended population. Further and significantly, the intended populations are not overlapping.

The requirement is still deemed proper and is therefore made FINAL.

4. Claims 2, 16, 17 and 19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventive groups, there being no allowable generic or linking claim. The non-elected peptides in Tables 11-29 of Claim 1 are

withdrawn. The non-elected antigens of Claim 13 are withdrawn. Applicant timely traversed the restriction and election requirements in the reply filed on 2/23/07.

5. Claims 1, 3-15 and 18 are all the pending claims under examination.

Oath/Declaration

6. The Oath/Declaration of 4/4/05 is objected to for the following reasons:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

See signature pages 2 and 3 where hand-written notes and underlined text appears. Applicants are invited to verify the objected text in the document on the PAIR system.

Priority

7. Priority claims to provisional applications 60/417,269 and 60/416,207 is acknowledged for the elected peptide sequences.

Specification

8. The abstract of the disclosure is objected to because the abstract is a virtual copy of the cover page from the corresponding WO 2004/031211 application. Correction is required. See MPEP § 608.01(b).

9. The specification is objected to because it does not provide sequence identifiers for the peptide sequences of $\geq$ four (4) amino acid residues in length pursuant to 37 CFR 1.821 (c) and/or (d): see Tables 5, 6 and 11-29.

Applicants are required to identify the above-referenced peptide sequences with sequence identifiers in addition to any other peptide or nucleotide (≥ ten (10) nucleic acids in length) sequences that may not be properly identified any in the specification.

10. The legend to Figure 1 is objected to because it does not recite the sequence identifiers for the anchor residues having ≥ four (4) amino acid residues shown in Figure 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1, 3-15 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 1, 3-15 and 18 are indefinite for reciting "peptides" because in Claim 1 it is not clear what the metes and bounds of the size of the peptide is. In [0064], the term "peptide is defined as "limited" when it has 100% homology to natural sequences but it is not clear how it is limited to be smaller or different. The claims are considered to read on any sequence that comprises the elected peptides or epitopes of SEQ ID NOS: 53, 55, 139, 502, 527, 627, 673, 807, 846 and 859.

b) In Claims 3 and 5, the phrase "HLT epitope" is not defined by the claims or in the specification and it is not clear what the metes and bounds of the phrase are with respect to the overall composition.

c) Claims 3-5 and 8 are indefinite because it is not clear how the HTL and CTL epitopes and the MHC targeting sequence are related to the peptides of Claim 1. For example, are the HTL and CTL epitopes admixed or joined to the peptides, or are they the same as some of the peptides of Claim 1? It is not clear what the metes and bounds of the CTL and HTL epitopes and the MHC targeting sequence are with respect to the peptides of Claim 1 or the overall composition.

d) Claims 1, 6, 7 and 9 are indefinite as to how the "spacer molecule" (Claim 6), "carrier" (Claim 7) and "lipid" (Claim 9) relate to the peptides of the composition of Claim 1. Is the spacer molecule conjugated to the peptides in order to link the peptides or does the spacer molecule serve to link a peptide to the lipid? Or does the spacer molecule serve as bridge between a peptide and a carrier? What is the intended meaning of the carrier:- is the carrier a solid support [0070] or an aqueous solution [0092]?

e) In Claims 11 and 12, the terms "heteropolymer" and "homopolymer" are not defined in the specification and it is not clear what the metes and bounds of the terms are with respect to the overall composition.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

12. Claims 3-5, 8, 11 and 12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to practice the invention as claimed.

Nature of the Invention

Claims 3-5, 8, 11 and 12 are drawn to the composition comprising one or more peptides of SEQ ID NO: 53, 55, 139, 502, 527, 627, 673, 807, 846 and 859, where at least one of the peptides is an HTL epitope or a CTL epitope or the composition comprises both an HTL epitope or a CTL epitope, where the composition comprises an

MHC targeting sequence, or where the peptides are a homopolymer or a heteropolymer.

Disclosure in the Specification

The specification does not show that any of the elected peptides (SEQ ID NOs: 53, 55, 139, 502, 527, 627, 673, 807, 846 and 859) has any of the claimed functional properties, namely, CTL-induction, HTL-induction or MHC targeting. The specification does not provide a single working example for any one of the elected peptides demonstrating that the peptide has one or more of the claimed functional properties in a relevant bioassay or animal model. The specification is not enabling for the peptides being heteropolymers or homopolymers because the specification does not define the structure or function for any of these molecules, or show how these molecules could be used.

Status of the Prior Art for T-immunogenic, MHC-binding Peptides/ Unpredictability/ Undue Experimentation

In general, the art of synthesizing functional equivalents of naturally occurring proteins is very unpredictable in nature. Although Schirle et al. (J. Immunol. Methods. 2001; 257: 1-16), for example, teaches that several computer algorithms are now available for use in predicting the structures of synthetic peptides that bind MHC molecules, Schirle et al. teaches, "the identified epitopes still have to pass the ultimate test: they have to prove to be useful in the in vivo situation" (page 11, paragraph bridging columns 1 and 2).

Moreover Anderson et al. (Tissue Antigens. 2000 Jun; 55 (6): 519-531) teaches there is poor correspondence between predicted and experimental binding of peptides to class I MHC molecules; see entire document (e.g., the abstract). Andersen et al. teaches, while knowledge of the peptide binding motifs of individual class I MHC molecules permits the selection of potential peptide antigens, there is no strong correlation between actual and predicted binding when using predictive computer algorithms, and therefore the peptide binding assay remains an important step in the identification of cytotoxic T lymphocyte (CTL) epitopes, which cannot be substituted by predictive algorithms (abstract).

Furthermore, Feltkamp et al. (Mol. Immunol. 1994 Dec; 31 (18): 1391-1401) teaches, while efficient binding of peptide epitopes to MHC class I molecules is required to elicit an immune response against the peptide epitope or the intact antigen, an increased binding affinity does not consistently and reproducibly relate to a peptide epitope's immunogenicity, i.e., its ability to elicit a peptide- and antigen-specific immune response; see entire document (e.g., the abstract). Feltkamp et al. teaches that other factors, in addition to its binding affinity for an MHC molecule, determine whether a peptide epitope, or analogue thereof, will be able to stimulate an effective immune response; see, e.g., the abstract.

With respect to the general state of the art for peptide induction of CTLs, Beier et al. (USPN 2004/0037840; published 2/26/2004; filed 10/26/2001) discloses:

> "It has been clearly demonstrated by several groups that tumour specific cytotoxic T cells (CTL's) are present in many tumours. These CTL's are termed tumour infiltrating lymphocytes (TIL's). However, these cells are somehow rendered non-responsive or

> anergic by several different possible mechanisms including secretion of immunosuppressive cytokines by the tumour cells, lack of co-stimulatory signals, down regulation of MHC class I molecules etc. There has been many attempts to isolate the tumour specific HLA class I bound peptides recognised by TILs, and in some cases it has also been successful (e.g. peptides from the melanoma associated antigens). Such peptides have been used to induce a tumour specific immune response in the host, but the practical use of tumour specific peptides in vaccines is restricted to a limited segment of the population due to the narrow HLA class I binding specificity of the peptides. Furthermore, it is usually relatively difficult to evoke a CTL response in vivo using synthetic peptides due to the low biological half-life of these substances as well as the difficulties with exogenous priming of MHC class I molecules." [0023-0024]

Applicants have not answered these questions in the specification or advanced our understanding of the status of the art for the inventive peptides with respect to these inherent risks associated with T-cell immunogenic peptides in general.

13. Claims 14 and 15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims,

the quantity of experimentation which would be required in order to practice the invention as claimed.

Nature of the Invention

Claim 14 is drawn to a pharmaceutical composition with an intended use to prevent a disease or disorder, and Claim 15 is drawn to a vaccine composition.

Disclosure in the Specification

The specification does not support the use of the papilloma virus peptide-based composition as a vaccine.

The term "vaccine" by definition implies any preparation intended for active immunological prophylaxis; e.g., preparations of killed microbes of virulent strains or living microbes of attenuated (variant or mutant) strains; or microbial, fungal, plant, protozoal or metazoan derivatives or products (see attached definition from Stedman's Medical Dictionary). Although just about any protein when inoculated can cause an immune reaction, the prophylactic nature of this reaction is not guaranteed and has come to be experimentally determined. Prophylaxis is defined as the prevention of disease or of a process that can lead to disease. This is achieved by use of an antigenic (immunogenic) agent to actively stimulate the immunological mechanism, or the administration of chemicals or drugs to members of a community to reduce the number of carriers of a disease and to prevent others from contracting the disease. The specification describes the elicitation of CTL responses. There is insufficient evidence that such a study would correlate with in vivo efficacy in humans.

Applicants have not provided any evidence showing protective peptidogenic-specific CTL or HTL induction in any animal model recognized as a human disease correlate much less in preventing papilloma virus infection or papilloma virus-mediated cancer. In the absence of working examples, one skilled in the art could not even predict and extrapolate that any peptide or a composition comprising at least one peptide, could reproducibly induce a specific T cell response in any healthy animal or patient much less in preventing an animal or patient from developing a disease or disorder associated with papilloma virus. Further Applicants have not shown that inclusion of widely differing peptides/epitopes in a composition comprising a multiepitope composition could reproducibly trigger polyspecific CTL and/or HTL responses in addition to MHC targeting in order to prevent a disease or disorder occurring from papilloma virus.

Applicants are invited to supplement the record with evidence showing a correlative effect for any vaccine composition or any pharmaceutical composition comprising a multiepitope polypeptide in producing MHC -restricted, epitope-specific CTL and HTL induction as broadly encompassed by the claims.

Status of the Prior Art for Papilloma Virus Vaccines

It is well known in the art that papilloma virus peptides can elicit certain MHC/CTL and MHC/HTL responses. The art does not provide examples to show that what works in vitro will also work in vivo. Azoury-Ziadeh (Viral Immunol. 12(4):297-312 (1999); describes an E6 THL epitope that induced T helper cell proliferation in vitro when LNC from mice immunized with whole E6 protein were challenged with the

peptide/ epitope) and Murakami (Can. Research 59:1184-1187 (1999); describes two (2) E7 CTL epitopes that induced CTL cell proliferation when LNC from mice immunized with a whole E6/E7 fusion protein were challenged with each of the peptide/epitope) are cited as examples that while use of peptide antigens are well known, there is no showing that results in vitro will follow in vivo to result in a vaccine.

Recent advances in human papilloma vaccine therapy in humans show great promise (Adams et al. (Vaccine 25:3007-3013 (2007)) but none of the commercial vaccines are peptide based as instantly claimed. Further in order to provide protection against greater than 90% of human papilloma virus types responsible for cervical cancer a vaccine would have to contain LI capsid virus-like particles for the eight most prevalent types of high risk human papilloma viruses, and the prevalence of these high risk HPV types is as follows: HPV 16 (53%), HPV 18 (17.2%), HVP 45 (6.7%), HPV 31 (2.9%), HPV 33 (2.6%), HPV 52 (2.3%), HPV 58 (2.2%) and HPV 35 (1.4%) (see p. 3009, Col. 1, ¶2-3 of Adams).

Undue experimentation is required to demonstrate a CTL and HTL response to just any peptides under in vitro much less in vivo conditions

The goal of tumor vaccination is the induction of tumor immunity to prevent tumors, tumor recurrence and to eliminate residual disease. Ezzell (J. NIH Res, 1995, 7:46-49) reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph) and further states that no one is very optimistic that a single peptide will trigger an immune

response strong enough to eradicate tumors or even to prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (p 48, ¶6).

The Examiner appreciates that "some experimentation does not necessarily equate to undue experimentation", but for Applicants to advance the peptides disclosed in the specification as being CTL and HTL-specific vaccines, would require in vitro bioassay(s) testing, in vivo animal testing and perhaps even clinical trials in human patients, which is not routine experimentation (MPEP 2164.06, "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (In re Wands, 858 F.2d 731, 737, 8 USQP2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

Conclusion

Applicants have not provided sufficient guidance in the specification to allow one skilled in the art to practice the claimed invention without undue experimentation. In the absence of such guidance and evidence, the specification fails to provide an enabling disclosure.

Conclusion

14. No claims are allowed.

15. The Examiner's search of the peptides of SEQ ID NOS: 53, 55, 139, 502, 527, 627, 673, 807, 846 and 859 in commercial protein sequence databases did not identify a single protein or peptide having 100% identity or homology with any one of the sequences. Thus the peptide sequences appear to be free of prior art.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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